REMARKS/ARGUMENTS

By this Amendment, claims 38, 50, 53, 56-57, 61-62, and 64 are amended, and claims 43, 51, 52, and 61 are canceled. Claims 46-48, 50, 66-71, and 74 have been withdrawn from consideration pursuant to a restriction requirement. Claims 38-42, 44-50, 53-57, 59-60, 62-74 are pending. Claims 38-42, 44-45, 49, 53-57, 59-60, 62-65, 72-73 are under consideration.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2004/0265350.

Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: support for the amendment to claim 38 for the limitations wherein the carrier has a density less than 40%; and the rate of release of the second material from the carrier is controlled by having the second material located within the pores in a degradable support, can be found in ¶[0030], ¶[0075], and ¶[0076]. Claim 53 has been amended in line with Claim, 38, on which it is dependent.

Claim 64 has been amended to remove the limitation that the carrier comprise block hydroxyapatite, to broaden the limitation that the carrier have a density of 30% theoretical, and to introduce the limitation that the release of MTX from the pores be controlled by having the MTX located within the pores in a degradable support. Basis for these amendments is found throughout the published specification, and specifically in paragraphs ¶[0030], ¶[0075] and ¶[0076].

Claim 62 has been amended to correct a typographical error.

Claims 41, 53, 56 and 57 have been amended to improve clarity and form in lieu of the

amended Claim 38, and to become dependent directly on Claim 38.

Claims 43, 51, 52 and 61 are cancelled without prejudice to the subject matter therein contained.

Applicants hereby affirm their prior election with traverse of Group I, claims 38 to 73, and further elected the species chemotherapeutic agents, specifically MTX, reserving their rights under 35 U.S.C. § 121 to file a divisional application for the nonelected claims.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejection under 35 USC 112 second paragraph

Claim 61 stands rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has cancelled Claim 61, without prejudice to the subject matter contained therein, in order to expedite the allowance of this application. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102(b)

Claims 64 and 65 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Itokazu et. al. (J. Biomed. Mater. Res., 1998, 39, p. 536 - 538). This rejection is respectfully traversed.

The Examiner argues that independent claims 64 and 65 do not recite the identity of the ceramic carrier (i.e. does not distinguish between hydroxyapatite and ß-tricalcium phosphate or

any other ceramic). In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Itokazu reference. However, Applicant submits that this rejection is overcome by the present amendment to Claim 64. Itokazu does not teach the location of MTX, in a degradable support, within the pores of a porous ceramic article. Itokazu rather teaches the introduction of MTX into a porous apatite ceramic (PAL) in just a phosphate-buffered saline solution (page 2, 2nd paragraph). Hence, amended claim 64, and the claims dependent therefrom, are not anticipated by the disclosure of Itokazu, because Itokazu does not disclose each and every feature of the claim.

Accordingly, reconsideration and withdrawal of the rejection of claims 64 - 65 under 35 USC 102(b) is respectfully requested.

Pending claims 38 – 42, 44, 62- 63, 72 and 73 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Imura et al. (US 6,340,648). This rejection is respectfully traversed.

The Examiner argues that the Imura reference teaches that a calcium phosphate porous sintered body, including hydroxyapatite, having pores of a size within the claimed range and a porosity of 55% or more and 90% or less (i.e. a theoretical density of 10 - 45%), which is

allegedly anticipatory to applicant's ranges of less than about 30%, as in instant claim 38, or from about 10 to about 30%, as in instant claim 44.

In the instant case, not every element of the claims is present in the Imura reference because Imura describes a sintered porous calcium phosphate body which may be used for gradually releasing chemical material ('648 Imura at column 3, lines 32 to 35). Imura does not teach that the chemical material be located within the pores in a degradable support. Instead, Imura teaches that the entire calcium phosphate body is biodegradable ('648 Imura at column 7, lines 5 to 12). Since this limitation is not disclosed by the '038 Imura patent, the claims are not anticipated.

Accordingly, reconsideration and withdrawal of the rejection of pending claims 38 – 42, 44, 62- 63, 72 and 73 under 35 USC 102(b) is respectfully requested.

Pending claims 38–42, 44-45, 59, 62 - 63, 72 and 73 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Smith et al. WO 98/15505. This rejection is respectfully traversed.

The Examiner argues that Smith discloses porous ceramic articles, and that the articles are preferably prepared from hydroxyapatite (page 8, line 17). The Examiner further alleges that Smith teaches that pore sizes may range from 50 - 150 microns or greater than 150 microns (page 8, lines 6 - 7 and claim 14), and that the pore sizes in the formed article can be controlled to yield a material with a pre-determined pore size and level of interconnectivity. The porosity

may be from 20% to 90% (page 9, line 16). However, here, not every element of the claims is taught in the Smith reference. The Applicant respectfully submits that this rejection has been overcome by the present amendment to Claim 38.

The Smith reference describes a porous hydroxyapatite carrier which may be implanted with drugs such that it acts as a slow release agent (pages 10 and 11). Little detail is given by Smith, and there is no disclosure that the drug material be located within the pores in a degradable support. Since this limitation is not disclosed by the Smith reference, the claims are not anticipated.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 45, 59, 61 - 63, 72 and 73 under 35 USC 102(b) is respectfully requested.

Rejection under 35 USC 103(a)

Pending claims 38–42, 44-45, 49, 62-65, 72 and 73 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Imura et al. (US 6,340,648) or Smith et al. WO 98/15505, in view of Itokazu et al. (J. Biomed. Mater. Res., 1998, 39, p. 536 - 538). This rejection is respectfully traversed.

The Examiner argues that it would have been obvious to one of ordinary skill in the art to utilize MTX as the drug which is deposited within the hydroxyapatite carriers of Imura or Smith, and that one would have been motivated to do so because Itokazu teaches similar chemotherapeutic agent loaded porous apatite ceramics to be useful to fill grafts after curettage of bone tumor, and one would have been motivated to utilize hydroxyapatite having a porosity within the claimed range as allegedly taught by Imura or Smith in order to achieve a carrier with

an optimal balance of a desirable MTX release profile and adequate mechanical strength because Imura and Itokazu both teach the importance of pore size and porosity in drug release and strength of the carrier

The claims are patentable over the combination of the Imura or Smith and Itokazu references for the following reasons. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). MPEP 2143. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)).

Here, Applicant submits that the rejection has been overcome by the present amendments to claims 38 and 64. Each of Imura, Smith and Itokazu describe calcium phosphate or hydroxyapatite porous carriers which may be used for the release of chemicals or drugs.

However, none of Imura, Smith or Itokazu, discloses locating a second material within the pores of the carrier in a degradable material.

The Examiner alleges that Itokazu teaches porous apatite ceramics (PAC), including ß-tricalcium phosphate (TCP) and hydroxyapatite for the sustained release of a chemotherapeutic, methotrexate (MTX) (abstract), and that the MTX was loaded into the pores of the ceramic carrier via centrifugation. However, while Itokazu teaches the loading of a chemotherapeutic agent, MTX, into the pores of a porous apatite ceramic, it does not teach or suggest locating a second material within the pores of the carrier in a degradable material to control its release.

In addition, while Imura discloses calcium phosphate porous sintered bodies it also does not teach or suggest locating a second material within the pores of the carrier in a degradable material.

Furthermore, the Smith reference does not teach or suggest an interconnected skeleton having pores the majority of which are in the range of from about 20 to about 800 micron, the carrier comprising block hydroxyapatite and having a density less than about 30% theoretical, that the pores contain a second material deposited therein, the rate of release of the second material from the carrier being controlled by having the second material in a degradable support.

Therefore, the combination of the Imura or Smith and Itokazu references does not teach or suggest every limitation of the claims. Since the combination of the references does not disclose or suggest all the limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 45, 49, 51,

52, 61 - 65, 72 and 73 under 35 USC 103(a) is respectfully requested.

Pending claims 38-42, 44-45, 53-54, 56-57, 59, 62-63, 72, and 73 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Genin et al. (US 6,767,550), in view of Imura et al. (US 6,340,648) or Smith et al. (WO 98/15505). This rejection is respectfully traversed.

The Examiner alleges that Genin teaches a hydroxyapatite based drug delivery implant for cancer treatment, and that sustained release of the anti-cancer agents may be achieved after implantation at targeted sites. The Examiner further alleges that the Genin reference teaches that the ceramic component of the implant may be tricalcium phosphate, hydroxyapatite, etc.

However, the Applicant respectfully submits that this rejection has been overcome by the instant amendment of Claim 38. The '550 Genin patent discloses the use of hydroxyapatite implants, which may be porous or dense ('550 Genin at column 6, line 35), for the delivery of anti-cancer agents. For instance, Genin describes a multilayered structure of pure and drug-loaded biomaterials for use as an implant for which the resorption rate is designed ('550 Genin at column 6, lines 19 to 21).

The '550 Genin patent does not, however, describe a porous hydroxyapatite carrier having a second material located within the pores in a degradable support. It is implicit within the possibility that the implant may be dense or porous that the drug is not held within the pores of the implant, even if there are pores present. In other words, if the drug were meant to reside in, and be released from, pores, then a porous structure would be described as essential. Instead, it is surely intended that the drug resides within the molecular structure of the carrier, be it

hydroxyapatite or otherwise. This is consistent with the further implication that the entire implant is required to be resorbed or degraded for the drug to be released. Such an implication is amply demonstrated in the Genin patent ('550 Genin patent at column 5, lines 57 to 60):

> Hydroxyapatite tri-calcium phosphate and amino acid antibiotic composite ceramics are some of the most biocompatible and bioresorbable synthetic hard tissue implant materials.

The invention as presently recited in Claim 38 provides a porous hydroxyapatite skeleton which does not need to undergo resorption in itself in order to release chemicals held within. This is achieved by locating those chemicals within pores in a degradable support. The term "degradable" in this context can be only sensibly construed to mean "more degradable than hydroxyapatite", as this is what allows the material to be released from the pores in a controlled manner. These deficiencies are not addressed by the Smith or Imura references. For a rejection under §103(a) to stand, one of Imura or Smith must lead one skilled in the art to the invention of Claim 38. While Imura discloses calcium phosphate porous sintered bodies, it does not disclose a porous hydroxyapatite carrier having a second material located within the pores in a degradable support. In addition, the Smith reference does not teach or suggest a porous hydroxyapatite carrier having a second material located within the pores in a degradable support. Neither of Smith or Imura are able to do this, however, as both, as described above, teach the use of porous hydroxyapatite as a means for drug delivery, but neither disclose placing the drug in a support, degradable or otherwise, within the pores. In fact, the only true link between the numerous degradable carriers described by Genin and the porous hydroxyapatite carriers described by Smith and Imura is afforded by the present invention. This is a clear sign that the rejection has

been formulated with the use of impermissible hindsight.

Therefore, the combination of the Genin, Imura and Smith references does not teach or suggest every limitation of the claims. Since the combination of the references does not disclose or suggest all the limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claims 38 - 45, 51 - 54, 56 - 57, 59, 61 - 63, 72, and 73 under 35 USC 103(a) is respectfully requested.

Pending claims 38–42, 44-45, 53-57, 59, 62-63, 72, and 73 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Genin et al. (US 6,767,550), in view of Imura et al. (US 6,340,648) or Smith et al. (WO 98/15505), in further view of Brem et al. (US RE 37,410). This rejection is respectfully traversed.

The Examiner alleges that Genin teaches a hydroxyapatite based drug delivery implant for cancer treatment. The Examiner further alleges that Imura discloses calcium phosphate porous sintered body which comprises spherical pores communicating with one another substantially throughout the body, and with a porosity between 55 - 90% (i.e. a theoretical density of 10 - 45%)(abstract). The Examiner further alleges that Smith discloses porous ceramic articles which are preferably prepared from hydroxyapatite and that Brem teaches biodegradable polymer matrices for the controlled local delivery of chemotherapeutic agents (abstract), and that examples of such biodegradable polymers include natural polymers such as collagen, gelatin, etc. or synthetic polymers, preferably CPP-SA.

The Examiner argues that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize a ceramic with a density within the claimed range in the drug delivery implant of Genin consisting of drug-containing and drug-free layers because Imura or Smith teach porous calcium phosphate bodies, such as hydroxyapatite, to be useful for such purposes, and alleges that it would have been further obvious to substitute CPP-SA for collagen as the bioresorbable material in the carrier of Genin because Genin teaches collagen .or bioresorbable polymers to be useful, and because Brem teaches that CPP-SA is a biodegradable polymer which may be used as a functional equivalent to collagen.

However, the Applicant submits that this rejection has been overcome by the present amendment to Claim 38.

The Examiner has cited Brem, as none of Genin, Smith or Imura discloses the use of CPP-SA as a biodegradable polymer for use in drug delivery (see pages 11 and 12 of the Official Action).

Brem discloses methods and devices for delivery of a chemotherapeutic agent, particularly to the brain (column 1, line 60 to column 2 line, 15). The devices consist of reservoirs which release a drug over an extended period of time while preserving its bioactivity (column 3, line 66 to column 4, line 5). Various biodegradable polymers, including CPP-SA are described as suitable for forming these devices. Brem is essentially a substitute for Genin, Smith and Imura, describing, as it does, a different apparatus for performing the same task, albeit in a differing field. Brem states that the polymers used need to be flexible (column 5, line 22), which one having ordinary skill in the art would attribute to its use in soft tissue, such as the brain. On

the other hand, Genin, Smith and Imura are each concerned with rigid inorganic networks such as hydroxyapatite, more suitable for implanting in or around bone. The two materials are clearly not interchangeable - rigid support in a bone is important just as a flexible matrix is when used in soft tissue. Accordingly, the skilled artisan would not be able to combine the teachings of Brem with that of Genin, Imura and Smith. As has been described above, none of Genin, Smith or Imura describe the locating of a material within the pores of a hydroxyapatite carrier in a degradable support. Brem does not provide this feature, or point to it in any way. In the absence of this teaching, even if one skilled in the art did combine the teachings of these documents, he would not arrive at the Invention recited in the claims in suit. Surely all that the skilled artisan would take from this combination would be the possibility of building an implant having a supportive hydroxyapatite layer and a drug-filled layer of CPP-SA. The remaining step of filling the pores of a porous hydroxyapatite support with a drug-filled biodegradable polymer is simply too great for the skilled artisan to make. Not only is it not described in the art, but doing so would clearly make huge difference to the release profile of the drug in question. In the prior art, the drug is either held loosely in the pores, as in Imura and Smith, or Is held within the microstructure of the support itself, as in Genin. Any link, therefore, between the CPP-SA support as described by Brem, the porous carriers of Smith and Imura, and the layered biodegradable delivery systems of Genin may be made only with the hindsight afforded by the present invention.

Therefore, the combination of the Genin and Imura or Smith, and Brem references does not teach or suggest every limitation of the claims. Since the combination of the references does

not disclose or suggest all the limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claims 38–42, 44-45, 53-57, 59, 62-63, 72, and 73 under 35 USC 103(a) is respectfully requested.

Pending claims 38-43, 44, 59-60, 62–63, 72 and 73 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Imura (US 6,340,648) in view of Hakamatsuka (US 5,318,779). This rejection is respectfully traversed.

The Examiner argues that it would have been obvious to one of ordinary skill in the art to include a collagen polymer on the porous calcium phosphate, including hydroxyapatite bodies of Imura having a porosity which is preferably in the range of 60 - 85% and pore size which is preferably from 100 – 4000 μm (column 2, lines 40 - 48) because such materials are allegedly useful as carriers for drug delivery and gradual release systems (column 1, line 9). The Examiner further argues that one would have been motivated to do so because Hakamatsuka specifically teaches that such an exterior coating layer can be used for further controlling release of a drug from a similar porous ceramic material.

However, Applicant submits that this rejection has been overcome by the present amendment to Claim 38. Hakamatsuka describes a porous ceramic carrier for drug delivery. The carrier has a coating that controls the release of the drug from the carrier by means of having a lower porosity than the carrier itself ('779 Hakamatsuka at column 2, lines 16 to 20). This

carrier is made from a ceramic such as tricalcium phosphate, which will decompose and be absorbed within the body - hydroxyapatite is not preferred, as it is hardly absorbed after decomposition ('779 Hakamatsuka at column 2, lines 33 to 50). Hakamatsuka does not describe the locating of a drug within the pores of a carrier in a degradable support. The '779 Hakamatsuka patent does not, therefore, lead the skilled artisan from Imura, which as described above also lacks such a teaching, to the invention recited in Claim 38.

Therefore, the combination of the Imura and Hakamatsuka references does not teach or suggest every limitation of the claims. Since the combination of the references does not disclose or suggest all the limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success. As Applicant has demonstrated above, the presently amended independent Claims 38 and 64 are new and not obvious in view of the art of record. The Applicant thus respectfully submits that Claims 37 to 42, 44, 45, 49, 53 to 57, 59 to 63, 65, 72 and 73 are also new and not obvious, by virtue of their dependency on Claims 38 or 64.

Accordingly, reconsideration and withdrawal of the rejection of claims 38-43, 44, 59-60, 62–63, 72 and 73 under 35 USC 103(a) is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.